MACROLIDE DURATION DOMAIN ICU ADMINISTRATION GUIDE

SECTION 1: REMAP-CAP MACROLIDE DURATION DOMAIN INTERVENTIONS

This domain examines the anti-inflammatory effects of the study macrolide antibiotics, it is not examining their antimicrobial activity. In this domain participants are randomised to receive:

- Standard course macrolide discontinued between day 3 and day 5
- Extended course macrolide for 14 days or hospital discharge, whichever occurs first

SECTION 2: INTERVENTION ALLOCATION REVEAL

As part of participation in the antibiotic domain, the patient will receive a macrolide. The macrolide your site has chosen is displayed on the randomisation allocation page.

The allocation status for a patient in the Macrolide Duration Domain is obtained by navigating to the Macrolide Reveal page on the study database. Reveal can occur any time after randomisation, until the end of study day 5 but should be done as soon as sufficient information is available. The information required is:

- The results of microbiological testing
- Agreement from the patient or legal representative to participate in the Macrolide Duration Domain
- Whether macrolide therapy has been ceased for more than 36 hours
- Whether the treating clinician believes that allocation to either of the two interventions is appropriate

SECTION 3: DOSING GUIDE

The dose, route and frequency of administration of macrolide antibiotics are not specified in the protocol but the following guidance is provided:

1. Initial IV administration is strongly preferred
2. The preferred IV macrolide is Azithromycin, but others may be substituted based on local practice
4. Erythromycin cannot be used as the macrolide in this domain

The doses specified are recommended minimum doses. These should be modified in accordance with local guidelines and/or practice.

Agent	Dose
Azithromycin	500mg daily
Clarithromycin	500mg daily
Roxithromycin	150mg q12hr

- The dose of all macrolides is the same for IV and enteral administration
- No dose adjustment is required for impaired renal function or if the patient is receiving renal replacement therapy
- A switch from IV to enteral macrolide is permitted once the patient is clinically improving, as determined by the treating clinician

In pregnant women: Azithromycin and Roxithromycin are preferred to Clarithromycin.

SECTION 4: DURATION OF MACROLIDE THERAPY

Duration of macrolide therapy is determined by the study allocation (3-5 vs 14 days). This duration is specified by the trial, regardless of any other changes to other antibiotics for the treatment of CAP or new infections.

If allocated to standard course, cease after 3 days or immediately if between 3-5 days. If allocated to extended course, prescribe for 14 days.

If the patient is discharged from the ICU to the ward prior to the last day of therapy:

1. Evaluate the patient's QT interval if continuous cardiac monitoring will not be continued
2. Prescribe any remaining duration of macrolide therapy on the medication chart
3. It is not the responsibility of ICU research or medical staff to ensure the macrolide is administered on the ward

Discontinue the macrolide **prior to the completed course, ONLY in the following scenarios:**

- The patient experiences a serious adverse event (SAE) that is thought to be related to the macrolide
- The treating clinician believes it is not in the patients best interest to continue (for example, new QT prolongation)

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SECTION 5: CONCURRENT CARE

Low dose erythromycin (up to 250mg q6h) to promote gastric emptying is permitted, but alternative agents should be used in preference.

Please refer to the *Antibiotic Administration Guide* regarding administration of additional antibiotics.

SECTION 6: WORK FLOW